*Rearrangement of 2,3,5,6-tetraphenylindenone oxide* (Ib). A solution of 394 mg. (0.00088 mole) of the oxide and 0.5 ml. (0.004 mole) of boron trifluoride ethereate in 20 ml. of benzene was allowed to stand at room temperature for 15 minutes. The reaction mixture was diluted with ether, washed with water, dried over magnesium sulfate, and concentrated. The product crystallized from a benzene–ethanol mixture as red-orange prisms, m.p. 220–225°, yield 133 mg. (34%). Two additional recrystallizations from a benzene–hexane mixture afforded the lactone IIb as light orange prisms, m.p. 226.5–229° Similar results were obtained when the isomerization was effected in an ethereal solution of boron trifluoride or by the procedures previously described.[3]

DEPARTMENT OF CHEMISTRY
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE 39, MASSACHUSETTS

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# Synthetic Schistosomicides. I. A Diphenylsulfide Analog of Miracil D

EDWARD F. ELSLAGER, MILLARD MAIENTHAL,[1,2] AND D. R. SMITH[1,3]

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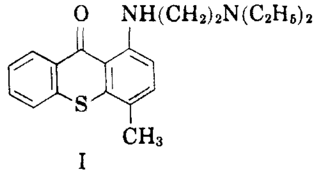
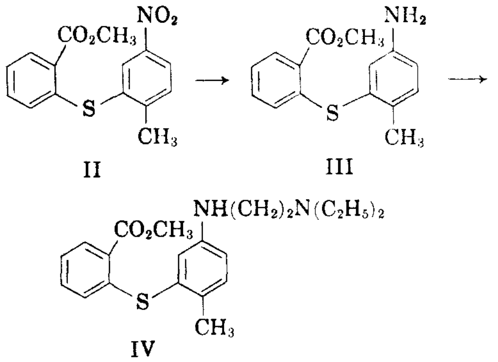
The development of Miracil D (I) in Germany during the recent war[4] represented a promising new lead in the field of schistosomiasis chemotherapy. The chemistry of Miracil D and some related compounds was published by Mauss in 1948,[5] while the biological and toxicological results were described in papers by Hawking,[6] Kikuth,[7] Vogel,[8] and Alves.[9] Further studies concerning related xanthenones and thiaxanthenones have been described in subsequent publications.[10–14]



I

In the course of studies directed toward the synthesis of compounds related to Miracil D, we have prepared methyl *o*-[5-(2-diethylaminoethylamino)-*o*-tolylmercapto]benzoate (IV), a diphenysulfide analog of Miracil D. The reaction sequence involved in its synthesis is indicated by formulas II through IV.



II III IV

Methyl *o*-(5-nitro-*o*-tolylmercapto)benzoate (II) was prepared by allowing the silver salt of methyl *o*-mercaptobenzoate to react with 2-iodo-4-nitrotoluene according to the method of Hammick,[12] or by the reaction of methyl *o*-chlorobenzoate with the silver salt of 5-nitro-*o*-toluenethiol. The latter mercaptan was synthesized by the following scheme: bis(5 - nitro - *o* - tolyl)disulfide was obtained by treating 5-nitro-*o*-toluenesulfonyl chloride with 50% hydriodic acid.[15] Reduction of the disulfide with potassium hydroxide and ethanol[16] yielded 5-nitro-*o*-toluenethiol, m.p. 52–53°, whose silver salt was readily prepared using ammoniacal silver nitrate in ethanol. Attempts to reduce the disulfide with a mixture of sodium hydroxide, ethanol, and sodium sulfide[17] yielded only an unworkable gum.

Reduction of the nitro ester (II) with Raney nickel and hydrogen gave 89% of methyl *o*-(5-amino-*o*-tolylmercapto)benzoate (III), which upon heating at 150–160° with freshly distilled 2-diethylaminoethyl chloride yielded methyl *o*-[5-(2-diethylaminoethylamino) - *o* - tolylmercapto]benzoate (IV). The ultraviolet absorption spectra of the ester IV in ethanol showed a band at 324 m$\mu$ ($\epsilon$ 8,000) and a band at 257 m$\mu$ ($\epsilon$ 22,000), with evidence of a stronger band at lower wave length. The infrared spectrum, run as a liquid film on a Beckman IR-2T Spectrophotometer, showed a band at 5.85 $\mu$ which is typical for a conjugated ester carbonyl, a week band at 2.94 $\mu$ which arises from an –NH– stretching vibration, and other prominent bands at 3.37, 6.26, 6.69, 6.87, 7.00, 7.76, 7.88, 8.02, 8.74, 9.04, 9.44, 9.67, 12.24, and 13.42 $\mu$.

The Miracil D analog IV was essentially inactive

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(1) Work done at James Millikin University.

(2) Bureau of Standards, Washington, D. C.

(3) Phillips Petroleum Company, Bartlesville, Oklahoma.

(4) Office of the Publication Board, Department of Commerce, Washington, D. C., Report No. 981.

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against *Schistosoma mansoni* in mice at a dose of 0.4% in the diet, and was inactive against a representative bacterial spectrum of eight organisms. It proved to be amebicidal against *Endamoeba histolytica* in an essentially protein-free medium at a concentration 40 µg./ml., while in the presence of gastric mucin it was amebicidal at a concentration of 200 µg./ml.[18]

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## EXPERIMENTAL

All melting points are uncorrected.

*5-Nitro-o-toluenesulfonyl chloride.* This compound was prepared by a modification of the procedure previously reported by Ullmann.[19]

A mixture of 50 g. (0.37 mole) of *p*-nitrotoluene and 178 g. (1.53 moles) of chlorosulfonic acid was gradually heated to 120° with mechanical stirring. This temperature was maintained for four hours, the mixture was allowed to cool, and the cooled mixture was slowly poured into a beaker containing 1 kg. of crushed ice and 1 kg. of water. The oily product was separated from the aqueous layer and was washed with water and dilute sodium bicarbonate solution. Distillation *in vacuo* gave 49 g. (57%) of light yellow crystals, b.p. 195–198°/20 mm., m.p. 43–45° (literature reports b.p. 183–185°/10 mm., m.p. 44.5°).[19]

*Bis(5-nitro-o-tolyl) disulfide.* A mixture of 49 g. (0.21 mole) of 5-nitro-*o*-toluenesulfonyl chloride and 160 ml. of 50% hydriodic acid was placed in a round-bottomed flask and heated gently.[15] After the initial exothermic reaction had subsided, the reaction mixture was refluxed for two hours. Upon cooling, the product which separated was collected by filtration, washed with dilute sodium bisulfite solution to remove excess iodine, washed with cold water, and dried *in vacuo.* Recrystallization from acetone gave 25 g. (71%) of cream-colored needles, m.p. 146–147°. A second recrystallization from 95% ethanol gave colorless needles, m.p. 148–151°.

*Anal.* Calc'd for $C_{14}H_{12}N_2O_4S_2$: C, 50.00; H, 3.60. Found: C, 50.24; H, 3.95.

*5-Nitro-o-toluenethiol.* This compound was prepared by a modification of the procedure described by Fromm and Wittmann[16] for the preparation of 4-nitrobenzenethiol.

A mixture of 9 g. (0.027 mole) of bis(5-nitro-*o*-tolyl) disulfide, 10 g. of potassium hydroxide, and 150 ml. of 95% ethanol was refluxed for 45 minutes. The reaction mixture was cooled and poured into an excess of ice-water with stirring. The resulting mixture was filtered, the filtrate was treated with Darco, and acidified with concentrated hydrochloric acid. The precipitate was collected by filtration and dried. Crystallization from 95% ethanol yielded 3.6 g. (40%) of red crystals, m.p. 51–54°.

Recrystallization from carbon tetrachloride (Darco) gave yellow crystals, m.p. 52–53°. The compound possessed a characteristic benzenethiol-like odor.

*Anal.* Calc'd for $C_7H_7NO_2S$: C, 49.68; H, 4.17. Found: C, 49.84; H, 4.39.

The silver salt was prepared by the addition of a filtered solution of 3.0 g. (0.018 mole) of 5-nitro-*o*-toluenethiol in 15 ml. of 95% ethanol to a solution of 3.5 g. (0.02 mole) of silver nitrate in 10 ml. of water, 3.5 ml. of ammonium hydroxide (*sp. gr.* 0.880), and 35 ml. of 95% ethanol. The resulting orange precipitate was washed thoroughly with water and 95% ethanol, collected by filtration, and dried *in vacuo* at 100°. The crude orange-yellow salt weighed 4.1 g. (95%), m.p. >250°. It was insoluble in water and common organic solvents, and was decomposed by hydrogen sulfide. The crude salt was utilized directly in the preparation of methyl *o*-(5-nitro-*o*-tolylmercapto)benzoate (II).

*Methyl o-(5-nitro-o-tolylmercapto)benzoate* (II). (*a*) A mixture of 4 g. (0.016 mole) of the crude silver salt of 5-nitro-*o*-toluenethiol, 2.8 g. (0.016 mole) of methyl *o*-chlorobenzoate, 0.5 g. of copper bronze, 0.2 g. of cuprous iodide, and 50 ml. of xylene was refluxed for eight hours. The mixture was cooled, filtered, and the xylene was removed *in vacuo.* The residue was recrystallized from benzene and cyclohexane, and yielded 1.1 g. (23%) of colorless prisms. m.p. 118–119° (literature reports m.p. 119°).[12]

(*b*). This compound was also prepared from 2-iodo-4-nitrotoluene and the silver salt of methyl *o*-mercaptobenzoate[12] in 65% yield, m.p. 119–120°. The melting point of a mixture of samples from procedures a and b was not depressed.

*Methyl o-(5-amino-o-tolylmercapto)benzoate* (III). A solution of 10 g. (0.033 mole) of methyl *o*-(5-nitro-*o*-tolylmercapto)benzoate (II) in 200 ml. of methyl alcohol was placed in a 500-ml. glass pressure bottle; 3 g. of freshly prepared Raney nickel was added, and the mixture was shaken on a Parr hydrogenation apparatus. The initial hydrogen pressure was 55.5 p.s.i.g., and the theoretical amount of hydrogen was taken up in seven hours. The catalyst was removed by filtration, the resulting solution was poured into an excess of water with stirring, and the colorless crystals which separated were collected by filtration. Upon drying, 8 g. (89%) of amine was obtained, m.p. 95–96°. Recrystallization from a water-methanol mixture yielded colorless crystals, m.p. 101–102°

*Anal.* Calc'd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.56. Found: C, 65.86; H, 5.43.

*Methyl o-[5-(2-diethylaminoethylamino)-o-tolylmercapto]-benzoate* (IV). A mixture of 5.5 g. (0.02 mole) of methyl *o*-(5-amino-*o*-tolylmercapto)benzoate (III) and 3.5 g. (0.026 mole) of freshly distilled 2-diethylaminoethyl chloride (b.p. 48°/16 mm.) was heated at 150–160° for two hours under nitrogen. An initial exothermic reaction was observed as the temperature reached 130°. Upon cooling, the mixture solidified, yielding a hard glassy material. This material was pulverized, made strongly alkaline by the addition of 4 *N* sodium hydroxide, and the mixture was extracted with four 100-ml. portions of ether. The yellow ether solution was dried over potassium carbonate for 12 hours, filtered, and the ether was removed *in vacuo.* The thick oily residue was distilled *in vacuo* in a 10-ml. distilling flask, yielding 3.1 g. (42%) of a viscous oil, b.p. 169–172°/0.4 mm.

*Anal.* Calc'd for $C_{21}H_{28}N_2O_2S$: C, 67.71; H, 7.58; N, 7.52. Found: C, 67.94; H, 7.37; N, 7.51.

PARKE, DAVIS & COMPANY
DETROIT, MICHIGAN
JAMES MILLIKIN UNIVERSITY
DECATUR, ILLINOIS

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(18) For a description of test methods, see P. E. Thompson, J. W. Reinertson, A. Bayles, D. A. McCarthy, and E. F. Elslager, *Am. J. Trop. Med. Hyg.*, **4**, 224(1955).

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